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Diabetic foot care knowledge and practice in type 2 diabetes and relation to microvascular complications in Alexandria (Egypt)

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Objectives. Egypt occupies the 8th rank in the prevalence of diabetes mellitus worldwide. The social and financial burden of diabetes and its complications represents a major health problem in Egypt. Diabetic foot and its consequences (ulcers and amputation) are preventable through good education for both physicians and patients.

Methods. This cross-sectional study was conducted on 100 patients with type 2 diabetes attending diabetes outpatient clinic in Alexandria main university hospital (AMUH). Patients were subjected to history taking, physical examination, and laboratory investigations. Screening for peripheral neuropathy was done using Michigan Neuropathy Screening Instrument (MNSI). A pre-tested questionnaire was used to assess the diabetic foot care knowledge and practice in participants.

Results. Only 25% and 24% of participants had good diabetic foot care knowledge and practice, respectively. There was a highly significant positive correlation between knowledge and practice in studied group ($p<0.001$). The presence of microvascular complications leads to a significantly higher knowledge, but not practice.

Conclusions. Diabetic foot care knowledge and practice are poor in our community. Foot care knowledge, unlike practice, is increased with the presence of microvascular complications. We should develop effective educational programs for patients and physicians to increase knowledge and practice before the development of complications.

Key words: diabetic foot care, knowledge, practice, microvascular complications, Egypt

The high prevalence of diabetes mellitus (DM) makes it a major health problem. This is due to an increased morbidity and mortality caused by its chronic complications (American Diabetes Association 2014). Type 2 diabetes (T2DM) represents more than 90% of cases of DM (Bandeira et al. 2013).

The estimated prevalence of diabetes in people aged 20–79 years was 151 million in the year 2000 and has risen to 463 million todays. Egypt occupies the 8th rank in the prevalence of diabetes worldwide with an estimation of 8.2 million patients. It is expected that the number will double by the year 2045. By that time, Egypt will jump to the 6th rank in diabetes prevalence (Saeedi et al. 2019). The prevalence of DM in Alexandria is estimated to be 16.7% (Khalil et al. 2018).

Microvascular complications are the leading causes of blindness, end stage renal disease, and lower limb amputation. Education plays a major role in delaying their development and progression (Chilelli et al. 2013). The prevalence of microvascular complications in patients with diabetes in Alexandria was 20% for peripheral neuropathy, 33.2% for diabetic kidney disease (DKD), and 34.6% for diabetic retinopathy (DR) (Khalil et al. 2019).

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Health education is a crucial component of diabetes care. It aims to better control and reduction of complications (Peyrot et al. 2009). Foot care education should be provided to both patients and health care providers in a regular manner (Bus et al. 2020). In Egypt, as an Islamic country, foot hygiene is done as a part of daily religious practice. But unfortunately, there is a lack of knowledge about the proper diabetic foot care.

Materials and methods

Ethical considerations. The current research has been carried out in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration in 1975 and its subsequent revisions. An approval has been obtained from ethics committee (EC) of the Institution. Each participant has signed a written informed consent before participating in this study.

Subjects. The study included 100 patients with T2DM aged between 18–65 years with duration of diabetes of at least 6 months. Patients with type 1 diabetes, pregnancy, and lactation were excluded. Patients were recruited from diabetes outpatient clinic in the period from June 2020 to September 2020. All patients attended the diabetes outpatient clinic in this period, fulfilling the inclusion and exclusion criteria, and accepting participation in the study were included. Recruitment of the patients was expected to be done within 2 months. However, due to COVID-19 pandemic, as a safety precaution, there was a reduction in outpatient clinics capacity to 50% of the total capacity. Patients with diabetes were afraid of attending health care facilities during this period for fear of infection. Thus, the period of recruitment was extended for another 2 months.

Clinical and biochemical data. All participants were subjected to full history taking including age, level of education, and duration of diabetes. Physical examination included vital signs (pulse and blood pressure) and anthropometric measures (weight, height, and waist circumference, WC). WC was measured according to WHO recommendations at the midpoint between highest point of the iliac crest and lowest point of the costal margin at the end of expiration. Body mass index (BMI) was calculated from the equation BMI = weight (in kg)/[height (in m)]^2 (Alberti et al. 2006). Fundus examination was done in ophthalmology outpatient clinic using slit lamp biomicroscope plus fundus lens by the same efficient ophthalmology specialist for all cases.

Diabetic foot examination was done for detection of peripheral neuropathy by Michigan Neuropathy Screening Instrument score (MNSI). MNSI is divided into two parts: MNSI questionnaire (MNSI A): It includes 15 "yes or no" questions. The maximum score of MNSI A is 13. MNSI clinical examination (MNSI B) including skin inspection, ankle reflex and vibration sensation. The total score of MNSI B is 8. Peripheral neuropathy was diagnosed when MNSI B is ≥2 (Feldman et al. 1994; Herman et al. 2012).

Laboratory investigations. After overnight fasting 8–12 hours, 5 ml of blood were withdrawn for measurement of HbA1c, fasting plasma glucose (FPG), and serum creatinine measurement. Estimated glomerular filtration rate (eGFR) was calculated using chronic kidney disease epidemiology collaboration equation (CKD-EPI), which is the preferred equation by American Diabetes Association. A spot urine sample was obtained for measurement of urinary albumin to creatinine ratio (UACR). Albuminuria was diagnosed if UACR was ≥30 mg/g. DKD was diagnosed by the presence of albuminuria and/or reduced eGFR <60 mL/min/1.73 m^2 (National Kidney Foundation 2013).

Questionnaire. Diabetic foot care knowledge and practice were assessed by using a pretested structured and validated questionnaire designed by Hasnain and Sheikh (2009), which is a set of 15 "yes or no" questions on knowledge and practice. Each "yes" answer carried one point and zero point for a "no". The questionnaire was translated into Arabic language by two independent native Arabic speakers. Then, backward English translation was done by two bilingual native English speakers. Then, this English backward translated version was compared with the original English version with no discrepancies. Content validity was assessed with an expert panel of 10 investigators, who agreed with the translated version. Internal consistency of knowledge and practice were evaluated by computing Cronbach's alphas coefficients, which were 0.90 for knowledge and 0.76 for practice. A pilot study was done to test the translated questionnaire on 10 patients prior to real study to ensure that the asked questions are understood by respondents with no needed modifications. Those patients were excluded from the study participants. The participant's knowledge and practices regarding foot care was classified as good, satisfactory or poor depending upon the score: good knowledge - if the score was more than 70% (11–15) points; satisfactory knowledge – if the score was 50–70% (10–8) points; and poor knowledge - scores were less than 50% (<8) points. The same classification was applied to practice.

Statistical analysis. The data were analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was used to verify the normality of distribution of variables. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). ANOVA was used for comparing the studied groups and followed by post hoc test (Tukey) for pairwise comparison. Kruskal-Wallis test was used to compare different groups for abnormally distributed quantitative variables followed by Dunn's post hoc test (for multiple comparisons) for pairwise comparisons. Spearman coefficient was used to correlate between quantitative variables. Significance of the obtained results was judged at the 5% level.

Table 1
Distribution of the studied population according to different parameters (n=100)

Parameter	Number (%)	Mean ± SD
Gender		
Male	59 (59%)	
Female	41 (41%)	
Age (years)		52.5±8.3
Education		
Low	41 (41%)	
Intermediate	26 (26%)	
High	33 (33%)	
Duration of Diabetes (years)		9.8±7.0
BMI (kg/m^2)		32.0±6.0
Waist circumference (cm)		90.9±8.6
Fundus examination		
Normal	69 (69%)	
Retinopathy	31 (31%)	
UACR		
Normal	70 (70%)	
Albuminuria	30 (30%)	
Total MNSI B		
Abnormal (>2)	58 (58%)	
Normal (≤2)	42 (42%)	
DKD		
Abnormal	39 (39%)	
Normal	61 (61%)	
Fasting blood glucose (mg/dl)		190±83.2
HbA1c (%)		8.7±2.0
Serum creatinine (mg/dl)		1.1±0.3
eGFR EPI (ml/min/1.73 m^2)		73.7±22.9
Total MNSI A		6±4.3
Total MNSI B		2.8±2.1

Abbreviations: SD – standard deviation; BMI – body mass index; UACR – urinary albumin to creatinine ratio; MNSI – Michigan Neuropathy Screening Instrument; DKD – diabetic kidney disease; HbA1c – glycosylated hemoglobin; eGFR EPI – estimated glomerular rate by epidemiology collaboration equation.

Results

The present study included 100 participants with T2DM. Baseline characteristics are shown in Table 1. The mean age of studied patients was 52.53±8.31 years. There were 59 males and 41 females. The mean duration of diabetes was 9.76±7.04 years. Regarding education level, 41 patients had low, 26 intermediate, and 33 high educations. Regarding microvascular complications, 58 patients had peripheral neuropathy, 31 DR, and 39 DKD.

Diabetic foot care knowledge was poor in 60%, satisfactory in 15% and good in only 25% of patients. The highest knowledge score was towards the importance of taking anti-diabetic treatment to prevent complication (97%), while the least knowledge score was towards daily washing of the feet (27%). Regarding practice, 43% had poor, 33% intermediate and 24% good practice. The highest practice score was for daily washing of the feet (90%) and the least was for inspection of feet daily by respondents (25%). The median score for knowledge and practice were 6 and 8, respectively (Table 2) There was a highly significant positive correlation between knowledge and practice in the studied group ($p<0.001$) (Figure 1).

Correlations of knowledge and practice with different parameters are shown in Table 3. There was a statistically significant positive correlation between the knowledge and the age, diabetes duration, BMI,

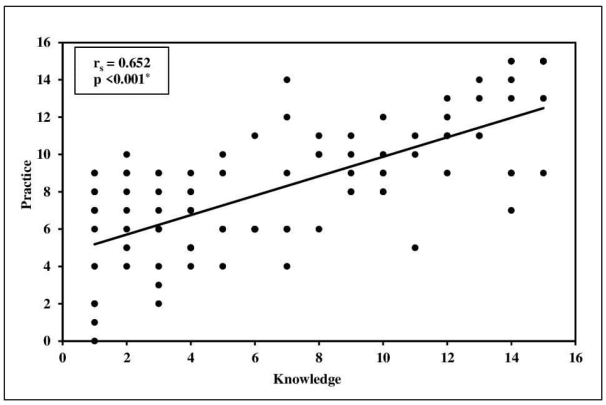

Figure 1. Correlation between knowledge and practice (n=100).

WC, serum creatinine level, and total MNSI A and B score, while there was a statistically significant negative correlation between the total knowledge score and the eGFR. Regarding practice, there was a statistically significant positive correlation between the practice, age, and WC.

Table 2
Distribution of the studied population according to knowledge and practice (n=100)

Parameter	Knowledge	Practice
1. Importance of taking anti-diabetic treatment to prevent complication	97 (97%)	65 (65%)
2. Daily washing of the feet	27 (27%)	90 (90%)
3. Using warm water for washing/bathing	41 (41%)	75 (75%)
4. Checking the temperature of the water before using	38 (38%)	66 (66%)
5. Drying the feet after washing	47 (47%)	59 (59%)
6. Talcum powder usage for keeping interdigital spaces dry	45 (45%)	44 (44%)
7. Keeping the skin of the feet soft to prevent dryness	30 (30%)	29 (29%)
8. Lotion not to be applied in the interdigital space	29 (29%)	42 (42%)
9. Daily change of socks	38 (38%)	63 (63%)
10. Trimming toe nails straight with care	56 (56%)	56 (56%)
11. Inspection of feet daily by respondents	41 (41%)	25 (25%)
12. Wearing comfortable coat shoes	59 (59%)	73 (73%)
13. Checking the inside of the shoes before wearing	33 (33%)	41 (41%)
14. Not walking barefoot	55 (55%)	50 (50%)
15. Warning signs for which consultation is required	48 (48%)	45 (45%)
Total score		
Poor (<8)	60 (60.0%)	43 (43.0%)
Satisfactory (8–10)	15 (15.0%)	33 (33.0%)
Good (11–15)	25 (25.0%)	24 (24.0%)
Median (Min.–Max.)	6 (1–15)	8 (0–15)
Mean ± SD	6.8±4.6	8.2±3.4

Abbreviations: SD – standard deviation.

Table 3
Correlation between knowledge and practice with different parameters (n=100)

Parameter	Knowledge		Practice	
	r_s	p-value	r_s	p-value
Age (years)	0.442	<0.001*	0.260	0.009*
Duration of Diabetes (years)	0.410	<0.001*	0.102	0.313
BMI (kg/m^2)	0.244	0.014*	0.129	0.200
Waist circumference (cm)	0.301	0.002*	0.213	0.033*
Fasting plasma glucose (mg/dl)	0.031	0.762	–0.088	0.386
HbA1c (%)	0.091	0.367	–0.138	0.170
Serum Creatinine (mg/dl)	0.283	0.004*	0.022	0.831
eGFR EPI (ml/min/1.73 m^2)	–0.381	<0.001*	–0.115	0.254
Total MNSI A	0.491	<0.001*	0.142	0.158
Total MNSI B	0.479	<0.001*	0.144	0.153

Abbreviations: r_s – Spearman coefficient; BMI – body mass index; HbA1c – glycosylated hemoglobin; eGFR EPI – estimated glomerular rate by epidemiology collaboration equation; MNSI – Michigan Neuropathy Screening Instrument.
*$p \leq 0.05$ – statistically significant.

Relations between subgroups of knowledge and practice with different studied parameters are shown in Table 4. There was no significant difference between subgroups of knowledge and practice regarding the education level, gender, and DKD. Regarding age, it was significantly higher in patients with good and satisfactory compared to those with poor knowledge and practice. Duration of diabetes was significantly higher in patients with good and satisfactory knowledge compared to patients with poor knowledge. Presence of retinopathy and albuminuria was significantly higher in good compared to poor knowledge patients' subgroups. Neuropathy was significantly higher in patients with satisfactory compared to poor knowledge subgroup. Fasting plasma glucose was significantly higher in patients with satisfactory compared to patients with good practice.

Discussion

Diabetic foot complications represent a major health and economic burden. It could be prevented by proper foot care education. The current study was conducted to assess the diabetic foot care knowledge and practice in T2DM in Alexandria, Egypt. Only 25% and 24% of patients had good knowledge and practice, respectively. Hasnain and Sheikh (2009) have also reported low knowledge and practice prevalence in their participants (29% and 14%, respectively). Muhammad-Lutfi et al. (2014) have also reported that the majority of patients had poor knowledge and practice. Magbanua and Lim-Alba (2017), in agreement with our results, have reported good practice in only 22.4% of patients, but on the other hand, the majority of patients had good knowledge (82.7%). This difference may be due to the presence of good and effective educational programs in their community. The previous three studies (Hasnain and Sheikh 2009; Muhammad-Lutfi et al. 2014; Magbanua and Lim-Alba 2017) have used the same questionnaire of the present study, but translated into different languages. Other studies (Desalu et al. 2011; Gautam et al. 2015; Ahmed et al. 2019; Pourkazemi et al. 2020) have also reported poor knowledge and practice in the majority of patients. On the other hand, a study in other country reported good foot care knowledge and practice (George et al. 2013). Ramirez-Perdomo et al. (2019) have found poor knowledge but better practice in the studied participants. Moreover, Manickum et al. (2021) have reviewed 58 studies on the diabetic foot care knowledge and practice and concluded that many people with diabetes have good knowledge but fewer have good practice. These differences between studies depend mainly on the presence of good educational programs in some countries and the use of different questionnaires.

Table 4
Relation between knowledge and practice categories with different parameters

Parameter	Total score knowledge			Total score practice		
	Poor (<8) (n=60)	Satisfactory (8–10) (n=15)	Good (11–15) (n=25)	Poor (<8) (n=43)	Satisfactory (8–10) (n=33)	Good (11–15) (n=24)
Level of education						
Low	26 (43.3%)	7 (46.7%)	8 (32%)	21 (48.8%)	12 (36.4%)	8 (33.3%)
Intermediate	13 (21.7%)	6 (40%)	7 (28%)	8 (18.6%)	11 (33.3%)	7 (29.2%)
High	21 (35%)	2 (13.3%)	10 (40%)	14 (32.6%)	10 (30.3%)	9 (37.5%)
χ^2(p)	4.678(^{MC}p= 0.327)			3.063 (0.547)		
Fundus examination						
Normal	48 (80%)	9 (60%)	12 (48%)	31 (72.1%)	22 (66.7%)	16 (66.7%)
Retinopathy	12 (20%)	6 (40%)	13 (52%)	12 (27.9%)	11 (33.3%)	8 (33.3%)
χ^2(p)	9.116* (0.010*)			0.337 (0.845)		
SBC	$^{FE}p_1$=0.173, p_2=0.003*, p_3=0.462					
Fasting plasma glucose						
Mean ± SD (mg/dl)	191.8±91.8	201.2±79.8	179.1±62.5	190.6±91.6	214.1±84.1	156±50.9
H (p)	0.726 (0.695)			6.460* (0.040*)		
SBC				p_1=0.180, p_2=0.145, p_3=0.011*		

Table 4
Continued ...

Parameter	Total score knowledge			Total score practice		
	Poor (<8) (n=60)	Satisfactory (8–10) (n=15)	Good (11–15) (n=25)	Poor (<8) (n=43)	Satisfactory (8–10) (n=33)	Good (11–15) (n=24)
DKD						
Abnormal	18 (30%)	7 (46.7%)	14 (56%)	16 (37.2%)	12 (36.4%)	11 (45.8%)
Normal	42 (70%)	8 (53.3%)	11 (44%)	27 (62.8%)	21 (63.6%)	13 (54.2%)
χ^2(p)		5.450 (0.066)			0.625 (0.731)	
Gender						
Male	35 (58.3%)	8 (53.3%)	16 (64%)	27 (62.8%)	18 (54.5%)	14 (58.3%)
Female	25 (41.7%)	7 (46.7%)	9 (36%)	16 (37.2%)	15 (45.5%)	10 (41.7%)
χ^2(p)		0.469 (0.791)			0.531 (0.767)	
Age (years)						
Mean ± SD	50.0±7.9	58.1±7.5	55.3±7.2	49.7±8.1	54.4±8.7	55.1±6.8
F (p)		8.632* (<0.001*)			4.771* (0.011*)	
SBC		p_1=0.001*, p_2=0.014*, p_3=0.515			p_1=0.036*, p_2=0.026*, p_3=0.940	
Duration of diabetes						
Mean ± SD	8.1±6.6	11.5 ± 6.2	12.8±7.4	9.1±7.3	10.0±6.4	10.6±7.6
H(p)		10.739* (0.005*)			1.088 (0.580)	
SBC		p_1=0.036*, p_2=0.003*, p_3=0.764				
UACR						
Normal	48 (80%)	10 (66.7%)	12 (48%)	32 (74.4%)	23 (69.7%)	15 (62.5%)
Albuminuria	12 (20%)	5 (33.3%)	13 (52%)	11 (25.6%)	10 (30.3%)	9 (37.5%)
χ^2(p)		8.698* (0.013*)			1.044 (0.593)	
SBC		$^{FE}p_1$=0.270, p_2=0.003*, p_3=0.251				
MNSI B						
Neuropathy (>2)	27 (45%)	14 (93.3%)	17 (68%)	25 (58.1%)	19 (57.6%)	14 (58.3%)
Normal (≤2)	33 (55%)	1 (6.7%)	8 (32%)	18 (41.9%)	14 (42.4%)	10 (41.7%)
χ^2(p)		12.876* (0.002*)			0.004 (0.998)	
SBC		$^{FE}p_1$=0.001*,p_2=0.053, $^{FE}p_3$=0.117				

Abbreviations: SD – standard deviation; SBC – significance between categories; χ^2 – Chi square test; FE – Fisher Exact; MC – Monte Carlo; F – F for ANOVA test, pairwise comparison bet. each 2 groups were done using Post Hoc Test (Tukey); H – H for Kruskal Wallis test, pairwise comparison bet. each 2 groups were done using Post Hoc Test (Dunn's for multiple comparisons test); DKD – diabetic kidney disease; UACR – urinary albumin to creatinine ratio; MNSI – Michigan Neuropathy Screening Instrument.
p – p-value for comparing between different categories; p_1 – p-value for comparing between Poor and Satisfactory; p_2 – p-value for comparing between Poor and Good; p_3 – p-value for comparing between Satisfactory and Good; * – Statistically significant at p≤0.05.

In the current study, the median knowledge score was 6, while the median practice score was 8. Perhaps this difference emerged from the fact that some practices were done for religious reasons and not from the proper knowledge of their importance for diabetic foot care. Surprisingly, analysis of answers of each question, discrepancies in answers of some questions between knowledge and practice in the same question favoring better practice were found. For example, the second question about daily washing of the feet had the least knowledge score (27%) and the best practice score (90%). This comes from the religious act of washing feet 5 times daily before prayers. Hasnain and Sheikh (2009) have shown similar results with better practice than knowledge regarding this question. This proves that patients are willing to perform good practice in the presence of knowledge and motivation. In contrary, other questions had better knowledge score than practice like the first question about importance of

taking anti-diabetic treatment to prevent complication. This could be improved on applying good and continuous education and follow up.

In a previous study (De Beradis et al. 2005), in more than 50% of patients, lack of physical examination of their feet by their treating physicians have been reported and 28% reported receiving no education. This may be due to crowded outpatient clinics and inadequate time for patients' education (Ang and Lim 2013). Thus, the process of diabetic foot care knowledge depends firstly on physicians.

The current study showed a statistically significant correlation between knowledge and practice as in agreement with Pourkazemi et al. (2020) and Goweda et al. (2017). Regarding the relation of knowledge and practice with level of education, we found no significant difference in diabetic foot care knowledge and practice in the studied patients in different educational levels. In agreement with the results of the present study, Muhammad-Lutfi et al. (2014) and Pourkazemi et al. (2020) have also found no difference in knowledge and practice compared with the level of education. On the other hand, Hasnain and Sheikh (2009) have reported higher knowledge and practice with higher level of education. This difference may be due to less diabetic foot education for well- and less-educated patients in our country.

The present study found a statistically significant positive correlation between age and total knowledge and practice score. Also, age was significantly higher in patients with good and satisfactory than with poor knowledge and practice. This may be due to that elderly frequently visit healthcare facilities for their comorbidities and chronic illnesses giving them better chance for education. Seid and Tsige (2015) have shown similar results. On the other hand, Muhammad-Lutfi et al. (2014) and Magbanua and Lim-Alba (2017) did not find significant relation between age, knowledge, and practice. This may be due to providing education for all age groups and different demographic data of the studied population. Regarding the gender, the present study did not find a significant difference between males and females regarding the foot care knowledge and practice. This is in concordance with the results of previous studies (Muhammad-Lutfi et al. 2014; Gautam et al. 2015; Magbanua and Lim-Alba 2017), which have reflected the equal opportunity for both sexes in attending healthcare facilities and obtaining education. On the other hand, Pourkazemi et al. (2020) have reported significantly higher knowledge in males than females.

We found significantly higher knowledge with prolonged duration of diabetes. Magbanua and Lim-Alba (2017) have also found higher knowledge and practice in patients with diabetes duration more than 10 years. In a study conducted by Hamidah et al. (2012) on patients with newly diagnosed diabetes, only 28.4% of patients practiced good habits towards foot care. Longer duration of diabetes allows patients to attend healthcare facilities more frequently and obtain better education. In disagreement with our results, Muhammad-Lutfi et al. (2014) have found no significant difference in knowledge and practice with duration of diabetes.

Regarding the microvascular complications, diabetic peripheral neuropathy, DR, and albuminuria were significantly higher in patients with good knowledge. There was also a statistically significant positive correlation between total knowledge score and MNSI A and B scores and a significant negative correlation between total knowledge score and eGFR. This may be due to frequently visiting health care facilities in the presence of complications, longer duration of diabetes, fear from bad consequences of these complications, and better chance for receiving education.

There were no significant relations between practice and microvascular complications. This goes with the attitude that after occurrence of complications patients seek knowledge to try to prevent progression and bad outcome. Magbanua and Lim-Alba (2017) have also shown that the knowledge is significantly associated with appearance of complication.

Li et al. (2014) have reported better foot care practice upon longer duration of diabetes and better knowledge on receiving education about complications. Saber and Daoud (2018), in discordance with the results of the present study, have reported significantly higher neuropathy in patients with poor knowledge score. A systematic review by Bonner et al. (2016) performed on 31 studies has concluded that diabetic foot ulcers and injuries are associated with poor diabetic foot care knowledge and practice in T2DM. To the best of our knowledge, this is the first study to discuss the relation between diabetic foot care knowledge and practice and the presence of microvascular complications other than peripheral neuropathy.

Conclusions

Diabetic foot care knowledge and practice are poor in our community. Foot care knowledge, unlike practice, is increased with the presence of microvascular complications. The reason may be that patients' awareness of foot care increases when they experience the complications. Foot care knowledge is positively

correlated to MNSI score. We should develop effective educational programs for patients and physicians to increase knowledge and practice before development of complications.

Study limitations. The present study has some limitations. It is a one center study. However, future multicentric studies are needed to generalize the results in different cohorts. Moreover, this is a cross sectional study. However, prospective follow up studies are required to assess the effect of education on increasing foot care knowledge and practice. Despite these limitations, the present study highlighted the low prevalence of good diabetic foot care knowledge and practice in Egypt, which requires an urgent action.

Conflict of interest: *The authors report no conflict of interest.*

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